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Soft-tissue fat tumours: differentiating malignant from benign using proton density fat fraction quantification MRI

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AIM: To evaluate if quantifying proton density fat fraction (PDFF) would be useful in separating lipoma, atypical lipomatous tumour (ALT) and liposarcoma in the extremities and trunk. In addition, differentiating ALT versus non-classical lipomas using magnetic resonance imaging (MRI)-based fatty acid composition (FAC) and three-dimensional (3D) texture analysis was tested.

MATERIAL AND METHODS: This prospective study (undertaken between 2014–2017; comprising 20 women, 21 men) was approved by the Regional Ethical Review Board and informed consent was obtained from all participants. For PDFF and FAC 3D spoiled gradient multi-echo images were acquired. PDFF was analysed in 16 lipomas (25–76 years), 14 ALTs (42–78 years) and 11 myxoid liposarcomas (31–68 years). The difference of mean PDFF was tested with one-way analysis of variance. A support vector machine algorithm was used to find the separating mean PDFF values.

RESULTS: Mean PDFF for lipomas was 90% (range 76–98%), for ALT 83% (range 62–91%), and for liposarcoma 4% (range 0–21%). The difference of mean PDFF for liposarcomas versus ALT and lipoma was significant (p=0.0001, for both), and for ALT versus lipoma (p=0.021). The optimal threshold for separating liposarcoma from ALT and lipoma was 41.5%, and for ALT and lipoma 85%. Texture analysis could not separate ALT and non-classical lipomas, while the difference for FAC unsaturation degree was significant (p=0.013).

CONCLUSION: Measuring PDFF is a promising complement to standard MRI, to separate liposarcomas from ALT and lipomas. Lipomas that are not solely composed of fat cannot confidently be separated from ALT using PDFF, FAC, or texture analysis.

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Introduction

Lipomatous tumours of the extremities and trunk are common in adults and can often be diagnosed by magnetic resonance imaging (MRI) without the need for biopsy.[1] The most common differential diagnoses are lipoma, atypical lipomatous tumour (ALT), and liposarcoma. Although other variants exist, such as hibernoma, angiolipoma, lipomatosis of nerve, lipomatosis, and lipoma arborescens, these are uncommon and rarely pose a diagnostic problem, except for the very rare hibernoma.[1,2] Lipomas rarely give symptoms, and do not have to be removed routinely. ALT do not metastasise and using this term rather than well-differentiated liposarcoma is advocated, as these tumours do not fulfil the definition of cancer. Moreover, as for lipomas, marginal surgical excision of ALT is adequate and disease-related mortality is essentially 0%.[3–5] On the contrary, the malignant fat tumour, liposarcoma, should be referred to a tertiary or sarcoma centre for surgical wide excision as well as radiation therapy in many cases; however, radiologists are not always confident in how to reliably differentiate benign from malignant fat tumours. Consequently, many benign fat tumours are referred as being suspicious for a malignant tumour. This poses an unnecessary workload for sarcoma centres as well as causing avoidable stress for the patient.

Fat tumours containing no or thin septa with homogeneous signal identical to subcutaneous fat on T1-weighted, T2-weighted, and fat-suppressed T2-weighted images, can with a high degree of certainty be characterised as lipomas. When the fat content is decreased, with thicker septa, or if other non-fat tissue is evident, the differentiation between lipoma, ALT, and liposarcoma is difficult, and the interpretation is susceptible to subjective assessment and the experience of the radiologist.[1,6] In two studies using visual assessment of fat percentage, only lipomas where found to have a fat content of 75–100%, while 1–75% fat content was found in lipoma, ALT, and liposarcoma; however, most of liposarcomas do not have any detectable fat on MRI.[6,7] Quantitative imaging would be preferable to eliminate subjectivity and interrater variability, and allow for safe diagnosis by even non-dedicated radiologists. The hypothesis in the present study was that benign and malignant fat tumours could be differentiated by quantifying the proton density fat fraction (PDFF) obtained with the Dixon technique.[8] The purpose was to simplify which fat tumours should be promptly referred to sarcoma centres. A further aim was to investigate if lipid metabolism and 3D texture analysis could be useful in differentiating these tumours.

Material and methods

Study participants

Patients referred to a sarcoma centre with a deeply located, i.e., subfascial, soft-tissue fat tumour in the trunk or extremities diagnosed on MRI or fine-needle aspiration biopsy were asked to participate in the study. The study was approved by the Regional Ethical Review Board and all participants signed a consent form. The aim, however, was to include approximately 10–15 patients each with a lipoma, ALT, and liposarcoma, and thereby conduct the study for approximately 2–3 years. Forty-one patients (20 females and 21 men) were enrolled in this prospective study between March 2014 and January 2017. All patients underwent surgery and had histopathological specimens reviewed by pathologists specialised in soft-tissue and bone tumours. Sixteen patients were diagnosed with lipoma (25–76 years; mean age 56), 14 patients with ALT (42–78 years; mean age 56), and 11 patients with a myxoid liposarcoma (31–68 years; mean age 44). The lipomas consisted of 12 regular lipomas, three lipomas with degeneration, and one lipoma with fat necrosis. PDFF was analysed in all 41 patients. MRI-based fatty acid composition was included in the study in October 2014 and was analysed in 29 patients (nine lipomas, 11 atypical lipomas, and nine myxoid liposarcomas).

MRI protocol

Patients were examined on a Siemens Verio 3 T system with coils used depending on tumour location in the body. For PDFF quantification, 3D spoiled gradient multi-echo images with 10 echoes were acquired. Relevant imaging parameters were: echo time (TE)1/ΔTE/repetition time (TR) = 1.88/1.84/21 ms, flip angle = 3° (to minimise T1 bias[9]), matrix = 128, field of view (FOV) = 256 mm (rectangular FOV and number of sections was varied based on anatomy and tumour extent), voxel dimensions = $2\times2\times2$ mm^3 and number of scan averages (NSA) = 1. A multi-scale graph-cut algorithm was used for Dixon-type fat–water separation and simultaneous R2*-mapping. For fatty acid quantification,[10] 3D spoiled gradient multi-echo images with 12 echoes were acquired. Relevant scan parameters were: TE1/ΔTE/TR = 1.80/1.55/21 ms, flip angle = 20°, matrix size = $96\times96\times48$, voxel dimensions = $2.7\times2.7\times5$ mm^3 and NSA = 12.

Data analysis

The tumours were segmented on PDFF maps for analyses of PDFF and tumour volume, aided when necessary by R2*-maps and conventional images, by a radiologist (M.S.) non-blinded to the histopathological diagnoses, with 16 years of experience at a sarcoma centre. For quantification of fatty acid carbon chain length (CL), unsaturation degree (UD; average number of double bonds [–CH=CH–] per triglyceride) and polyunsaturation degree (PUD; average number of double bond pairs separated by a single methylene group [=CH–CH_2–CH=] per triglyceride) histogram mode was chosen to reduce the sensitivity to low signal-to-noise ratio. 3D texture analysis using grey-level Haralick texture features was performed for the features homogeneity, entropy, correlation, cluster shade, and information measures of correlation 1 (IMoC 1).[11]

Statistical analysis

Statistical analysis was performed using SPSS software (version 24.0; SPSS, Chicago, IL, USA). Data are reported as means or medians as appropriate. The null hypothesis of no

significant difference of mean PDFF and tumour volume for lipoma, ALT, and myxoid liposarcoma was tested with one-way analysis of variance (ANOVA) and Bonferroni post-hoc analysis to correct for multiple comparisons. A support vector machine (SVM) algorithm was used to find the separating mean PDFF values for lipoma, ALT, and myxoid liposarcoma. For fatty acid composition and texture analysis of ALT versus lipoma independent Student's *t*-test was used. All tests were double-sided and *p*-values of <0.05 were considered to indicate a statistically significant difference.

Results

PDFF analysis

Mean PDFF for lipomas was 90% (range 76–98%), for atypical lipoma 83% (range 62–91%), and for myxoid liposarcoma 4% (range 0–21%; Fig 1). The difference in mean PDFF for liposarcomas versus ALT and lipoma was significant ($p=0.0001$, for both), as well as for ALT versus lipoma ($p=0.021$). PDFF maps and T1-weighted images of four cases (an ALT with PDFF 62%, a myxoid liposarcoma with PDFF 21%, a lipoma with PDFF 76%, and an ALT with PDFF 82%) are illustrated in Fig 2.

Using a SVM algorithm to find the separating PDFF values for the three groups, it was found that 41.5% was the optimal threshold for separating liposarcoma from ALT and lipoma with a precision of 1 and a sensitivity of 1. The precision for separating ALT and lipoma was optimal at 85%, with a precision and sensitivity of 0.73 and 0.57 for ALT, and 0.68 and 0.81 for lipoma, respectively. This is a limited data set, and the values should only be considered in an exploratory context. Mean PDFF for the lipoma with fat necrosis was 92%, for the three lipomas with degeneration it was 80, 86 and 89%, respectively, and for the remaining 12 lipomas it was 91.5% (range 76–98%).

Fatty acid composition

Six myxoid liposarcomas were excluded due to having none or minimal amounts of fat. As fatty acid composition was included 7 months into the study, there were fewer cases in comparison with the PDFF analysis. Nine lipomas, 11 ALT, and three myxoid liposarcomas remained for analysis of CL, UD, and PUD (Fig 1). As only three myxoid liposarcomas had detectable fat on MRI, these were excluded in the statistical analyses and the difference of UD mode for ALT versus lipoma was significant ($p=0.006$), but not for CL mode ($p=0.471$) or for PUD mode ($p=0.540$).

Tumour volume

Mean volume for lipomas was 237 cm^3 (3–600 cm^3; min–max), for ALT 265 cm^3 (14–714 cm^3; min–max), and for myxoid liposarcomas 218 cm^3 (30–805 cm^3; min–max). The difference for mean volume for lipomas, ALT, and myxoid liposarcomas was non-significant ($p=0.086$).

Subgroup analysis using 3D texture analysis and fatty acid composition

A common clinical problem is differentiating ALT versus non-classical lipomas (i.e., non-typical appearance on MRI). A subgroup analysis was therefore performed of ALT versus lipomas with PDFF <90%, using 3D texture analysis and MRI-based fatty acid composition. Patients included were three regular lipomas (mean FF 76%, 79% and 86%, respectively), three lipomas with degeneration (mean FF 80%, 86% and 89%, respectively), and 14 ALT (mean FF range 62–91%). No statistical significance ($P>0.05$) for homogeneity, entropy, correlation, cluster shade, or IMoC 1 was found. The difference for UD mode was significant ($p=0.013$), but not for CL mode ($p=0.157$) or for PUD mode ($p=0.495$).

Discussion

Differentiating soft-tissue fat tumours using standard MRI is difficult and leads to referrals of benign lipomas to sarcoma centres; however, by comparing the PDFF of liposarcomas, ALT, and lipomas malignant tumours could be differentiated from benign fat tumours. By using this objective measure, radiologists would be more confident in which fat tumours should be promptly referred to a sarcoma centre.

Differentiating malignant from benign tumours is essential in radiology and a common clinical scenario is to differentiate lipomas, ALT, and liposarcomas. Lipomas do not require treatment unless there is a cosmetic or functional

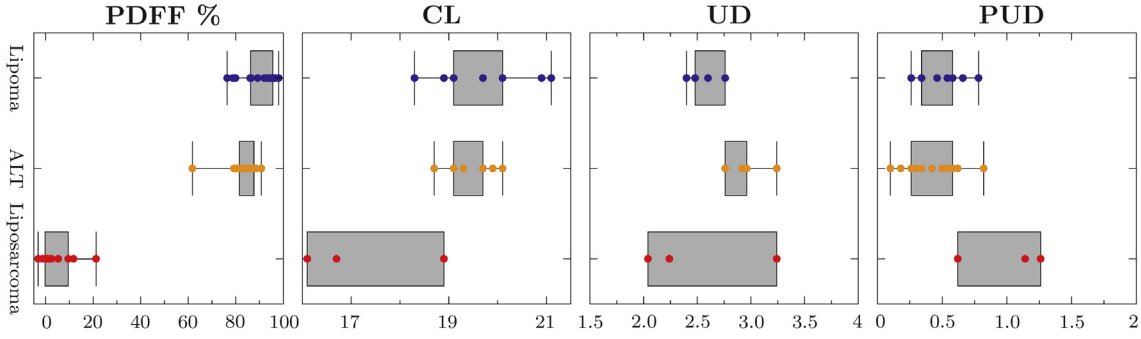

Figure 1 Lipoma (blue), atypical lipomatous tumour (orange), and myxoid liposarcoma (red). PDFF % and histogram mode for CL, UD, and PUD. Note that the modes are found on discrete levels due to the histogram binning.

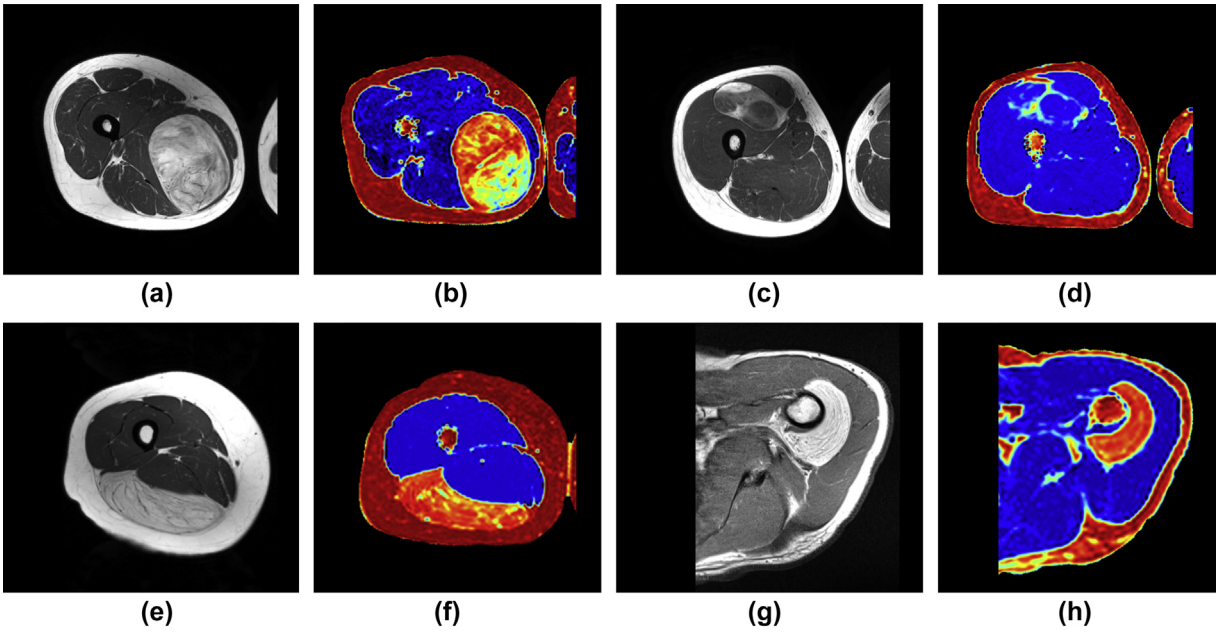

Figure 2 (a) T1-weighted image and (b) PDFF map (mean PDFF: 62%) of an atypical lipomatous tumour. (c) T1-weighted image and (d) PDFF map (mean PDFF: 21%) of a myxoid liposarcoma. (e) T1-weighted image and (f) PDFF map (mean PDFF: 76%) of a lipoma. (g) T1-weighted image and (h) PDFF map (mean PDFF: 82%) of an atypical lipomatous tumour.

problem. ALT are benign tumours that do not metastasise, with a low recurrence rate (9%) following surgery.[12] Transformation to dedifferentiated liposarcomas is even more uncommon in ALT, and if so, often occurs following several recurrences.[3,5,12] Myxoid, pleomorphic, and dedifferentiated liposarcomas are malignant and should promptly be referred for treatment at sarcoma centres; however, outside sarcoma centres there is often uncertainty among radiologists as to how to confidently interpret findings and not misdiagnose malignant fat tumours as benign. The reason may be that all studies have evaluated the visual grading of fat content, oedema and internal septa and/or nodules, which all are subject to experience of the radiologist and interrater variability.[1,5–7,13] To simplify this, objective measurements of PDFF were used, which have been shown to have high accuracy in differentiating malignant from benign vertebral compression fractures,[14] and could differentiate malignant from benign fat tumours. The highest fat content in a liposarcoma was 21%, whereas the lowest fat content in ALT was 62% and in lipomas 76%. Using an SVM algorithm 41.5% was an optimal threshold for separating benign from malignant tumours.

In the present study only lipomas had a PDFF >91% and using an SVM algorithm the precision for separating ALT and lipoma was optimal at 85%, although the study material is too small to adopt a cut-off value. A previous study visually grading fat tumours on standard MRI sequences found that no ALT had a fat content >75%.[7] On the contrary, in the present study all ALT except one had a PDFF >75%, which is accredited to the quantitative method. Most important clinically is to speedily refer malignant liposarcomas to sarcoma centres, without a biopsy or surgery. Management of ALT is under debate, many authors advocate surgery whereas others stress their benign nature. A further aim of the present study was to investigate whether MRI-based fatty acids or 3D texture analysis[15] could help in differentiating ALT from non-classical lipomas (i.e., lipomas not solely composed of fat, which included lipomas with PDFF <90%). Although UD mode was statistically significant for separating ALT and lipoma, it can be appreciated from Fig 1 that there is overlap between benign and malignant tumours, and this measure would not be useful clinically. Neither CL, PUD, texture analysis nor tumour size could be used to separate ALT and lipoma. In contrast to another study, ALT were not found to be larger in size than lipomas.[16]

Lipid metabolism is gaining interest in oncological research,[17] and carbon chain length, unsaturation degree, and polyunsaturation degree in these tumours were analysed. For both lipomas and ALT, measures were similar to subcutaneous fat tissue values, which have been estimated in a study by Berglund *et al.*[10] This puts further evidence into the benign nature of ALT. As most myxoid liposarcomas contain no fat, fatty acid could only be measured in three myxoid liposarcomas (containing 9%, 12%, and 21% fat); however, this low amount of fat reduces the precision in MRI-based fatty acid and might introduce bias, which therefore is insufficient for confident interpretation. In a previous article, the precision was increased by parameter reduction of UD,[13] albeit in this article the aim was to measure all three parameters. Even though these methods had limited clinical value, they may be useful in basic research of tumour metabolism and pharmacological studies.

A limitation of this study was that no cases of pleomorphic or dedifferentiated liposarcoma were included; however, pleomorphic have the lowest incidence of the liposarcomas and are known to have small amounts of fat.[4,18] Dedifferentiated liposarcoma is very rare and has a different radiological appearance, with two tumour components, one fatty

and one non-fatty.[4,18] Only subfascial fat tumours were included, as subcutaneous fat tumours are most often diagnosed using fine-needle biopsy and seldom pose a diagnostic problem. The aim of the present study was to obtain normative PDFF data on these tumours, and therefore, ROIs were placed non-blinded to ensure that the whole tumour was included and that non-tumour tissue was excluded. PDFF data was not compared to standard imaging, as evaluation of fat tumours is highly dependent on the experience of the radiologist, albeit experienced radiologists should be able to diagnose or suspect myxoid liposarcomas on conventional imaging. Finally, retroperitoneal fat tumours were not included as they are not handled by orthopaedic surgeons and have a different prognosis.

In conclusion, measuring PDFF is a promising complement to standard MRI, to confidently separate liposarcomas from ALT and lipomas, allowing the prompt referral of liposarcomas to sarcoma centres. ALT and lipomas that are not solely composed of fat cannot be separated using PDFF, MRI-based fatty acid composition or texture analysis. These patients may be referred to a sarcoma centre with standard priority, and should be informed of the benign nature of the tumour.

Conflict of interest

The authors declare no conflict of interest.

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The image platform PhONSAi (the medical Physics, Oncology and Nuclear medicine image research platform at Sahlgrenska Academy, Gothenburg, Sweden) was used for segmentation.

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